REMARKS

Claims 11-20 were pending prior to entering the amendments.

The Amendments

Claims 13, 14, 15, and 19 have been cancelled.

Claim 11 has been amended. This amendment incorporates limitations from the previously presented dependent claims 14, 15, and 19 which have been cancelled with this amendment. The addition of the limitation "wherein amino acids R484 and R585 belong to different capsid protein subunits" is supported by the specification at e.g., page 4, lines 14-17.

No new matter is added in the amendments. The Examiner is requested to enter the amendments.

The Response

Sequence Compliance – Drawings

In the current office action, the Examiner stated that: "The detailed description of Figure 1, should be amended to include the proper SEQ ID NO for the sequence depicted in Figure 1. However in their Response to Office Action dated January 30, 2008, Applicants properly amended the detailed description of Figure 1 with SEQ ID NO: 7. After a brief phone conversation with Applicants on July 15, 2008, the Examiner stated that this previous amendment was sufficient to overcome any objection based on Figure 1 and concluded that the pending objection was overcome.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claims 11 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the rejection, the Examiner stated that: "a skilled artisan would not necessarily know whether any AAV other than AAV-2 could be used in this invention." In response, Applicants have amended claim 1 so that it now recites "delivering to a patient an AAV-2 vector or an AAV particle having a capsid encoded by the AAV-2 vector." Thus, the basis for this rejection has been obviated by the amendment.

Additionally, in the rejection, the Examiner stated that the "limitation that the mutations must be on different capsid proteins" is an important feature requiring clarification. In response, Applicants have amended claim 11 with the limitation: "wherein amino acids R484 and R585 belong to different capsid protein subunits." Thus, the basis for this rejection has been obviated by the amendment.

In view of the above described amendments and remarks, Applicants request that the §112, second paragraph rejection be withdrawn.

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claim 11 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

In the rejection, the Examiner acknowledges that the specification is "enabling for a method of gene delivery of a double-mutant (R484E/R585E) adeno-associated virus to heart tissue." But the Examiner maintains that the specification "does not reasonably provide enablement for gene therapy (i.e., expression of a therapeutic gene in the target tissue such that an effective dose induces biological effect associated with improved health) for any tissue." The Examiner concludes that "it would require undue experimentation to practice the invention beyond the scope of a method of gene delivery of a double-mutant (R484E/R585E) adeno-associated virus to heart tissue."

Scope of the Invention

In response to the issues raised by the Examiners, Applicants have amended the method of claim 11 so that it covers "gene therapy in a heart muscle tissue" and delivering to a patient "an AAV-2 vector or an AAV particle having a capsid encoded by the AAV-2 vector" that comprises a heparin-binding motif of a capsid protein with a R484E/R585E double-mutant.

Guidance and Working Examples

In response to the Examiner's statement that the specification is enabling for "gene delivery" but not "gene therapy," Applicants wish to point out that in view of the current amendments to 11, Example 6 (specification at page 21-22) provides a working example of the claimed invention. As described in Example 6 and illustrated Figure 5, an AAV-2 vector

comprising R484E/R585E double-mutant not only successfully delivered a reporter gene (luciferase) to heart tissue *in vivo* but that the reporter gene activity (i.e., chemiluminescence) was expressed in the target heart tissue. The specification notes that the reporter gene activity "was surprisingly high in the heart sample suggesting heparan-sulfate independent transduction of heart tissue *in vivo* (Figure 5B). Thus, Example 6 illustrates that the method of claim 11, as currently amended, is reasonably enabled as a method of gene therapy because the specification illustrates its use to deliver a gene to the target tissue *in vivo* and demonstrate that the gene was expressed to produce a detectable and "surprisingly high" amount of protein. Clearly, one of ordinary skill in the art would reasonably consider the *in vivo* production of detectable amounts of a protein in a target heart tissue "therapeutic." Furthermore, although luciferase is not a therapeutic protein (as least as used here) Example 6 demonstrates that the method of claim 11 could be used without undue experimentation to deliver and express a therapeutic protein in heart tissue. The use of reporter genes such as luciferase to demonstrate successful functioning of gene delivery systems that can successfully allow gene therapy is well-established in this field.

State of the Art & Quantity of Experimentation

Applicants respectfully disagree with the Examiner's characterization of the state of the art of gene therapy. The Examiner's reliance on Verma et al. (1997) and Eck et al. (1995) as supporting the unpredictable state of the art of gene therapy is misplaced. These references from 1995 and 1997 do not provide probative evidence of the state of the art as of the 2003 priority date of the present application. In the intervening years, additional clinical trials using viral vectors for gene delivery have been conducted. For example, a quick online search revealed a 2003 review by Verma (Kootstra and Verma, "Gene Therapy With Viral Vectors," *Annu. Rev. Pharmacol. Toxicol.* 43, 413-39 (2003)) that describes how patients suffering from hemophilia were treated with AAV vectors expressing human factor X and this treatment showed some clinical benefits.

In view of the above-described amendments and remarks, Applicants believe that the bases for the Examiner's conclusion that undue experimentation would be required have been removed. Applicants respectfully request that the rejection be withdrawn.

Claim Rejections – 35 USC § 102

Claims 11-20 are rejected under 35 USC § 102(e) as allegedly anticipated by Warrington et al. (US2006/0088936, published April 27, 2006).

As currently amended, the method of independent claim 11 is directed to "gene therapy in a heart muscle tissue" and requires delivering to a patient an AAV-2 vector or an AAV particle having a capsid encoded by the AAV-2 vector that comprises a heparin-binding motif of a capsid protein with a R484E/R585E double-mutant. Warrington does not disclose (expressly or implicitly) or suggest the use of a R484E/R585E double-mutant. Consequently, Warrington does not anticipate claim 11, or its dependent claims 16-18, and 20, and the rejection of these claims should be withdrawn.

Claim Rejections – 35 USC § 103

Claims 11 and 15-20 are rejected under 35 USC § 103(a) as allegedly unpatentable over Bartlett et al. (US Pat. No. 6,962,815, issued Nov. 8, 2005) in view of Kaplitt et al. (US Pat. No. 6,162,796, issued Dec. 19, 2000) and further in view of Wu Xiao (PhD Dissertation 2002, University of Florida).

As currently amended, independent claim 11 is directed to a method of "gene therapy in a heart muscle tissue" and requires delivering to a patient an AAV-2 vector or an AAV particle having a capsid encoded by the AAV-2 vector that comprises a heparin-binding motif of a capsid protein with a R484E/R585E double-mutant. The cited combination of references fails to disclose (expressly or implicitly) or suggest to one of ordinary skill the R484E/R585E double-mutant required by the claims. Because the cited combination of references does not include every limitation of claim 11, the Examiner has not established a prima facie case of obviousness under 35 USC § 103(a) and the rejection should be withdrawn.

Even assuming the cited combination includes every limitation of claim 11, there is not a sufficient rationale to combine them because the results yielded by the proposed combination would not have been predictable to one of ordinary skill in the art at the time of the invention. As described in the present application, the R484E/R585E double-mutant "shows a similar loss

of cell binding and heparin binding" and was found to be "even more affected in it infectivity than the single mutants." (Specification at page 20, lines 10-12.) However, as shown by Example 6 (discussed above), the R484E/R585E double-mutant when delivered to heart tissue *in vivo* was expressed and produced a "surprisingly high" amount of protein. Because the results with the R484E/R585E double-mutant in heart tissue were unpredictable, the rationale that one of ordinary skill would have combined the reference to arrive at the claim is not sufficient to support an obviousness rejection. Furthermore, this unpredictable result underscores that one of ordinary skill would not have a reasonable expectation of success. The lack of a reasonable expectation of success causes any prima facie obviousness rejection based on the combination to fail.

In view of the above-described amendments and remarks, Applicants believe that the bases for the Examiner's obviousness rejection have been removed. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants have addressed the Examiner's new grounds of rejection provided in the Final Office Action dated April 16, 2008. Applicants believe that all pending rejections have been overcome and the claims are in condition allowance. Applicants respectfully request that the Examiner reconsider the application in view of the Applicants' remarks provided herein. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 798-3524.

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Respectfully submitted,

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